Generalized Cognitive Deficits in Schizophrenia

A Study of First-Episode Patients

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Background: Cognitive impairment is recognized as a core characteristic of schizophrenia. There has always been a debate about the nature, selectivity, and time of onset of these deficits in relationship to the onset of illness and treatment factors. To our knowledge, the present study represents the largest sample of mostly neuroleptic-naive patients with first-episode schizophrenia that has been reported to date.

Methods: A group of 94 patients experiencing their first episode of schizophrenic illness and 305 normal comparison subjects were administered a comprehensive clinical and neuropsychological evaluation. Seventy-three patients were neuroleptic naive, 14 had received treatment for less than 1 week, and the remaining 7 had been medicated for less than 2 weeks.

Results: Patients performed significantly worse than the comparison subjects on every neuropsychological variable except those assessing savings scores (ie, forgetting over time). Twenty-five of 30 tests had an effect size (ES) greater than 0.75 when the 2 groups were compared. An ES analysis within the schizophrenia group revealed that the greatest relative impairments were on the Wechsler Adult Intelligence Scale–Revised digit symbol (ES, −0.52) and comprehension (ES, −0.42) subscales.

Conclusions: Our findings are in concert with others demonstrating that significant cognitive impairment across multiple ability domains is a core characteristic of schizophrenia and is not caused by chronic illness, treatment, or institutionalization. The ES analysis emphasizes that patients with schizophrenia have a generalized deficit that is not easily explained by a single anatomical region or ability area.

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SUBJECTS, MATERIALS, AND METHODS

SUBJECTS

Patients were recruited from consecutive admissions to the general psychiatric ward and to the Mental Health Clinical Research Center, University of Iowa Hospital and Clinics, Iowa City, starting in 1982. After written informed consent was obtained, patients underwent comprehensive screening and assessment. Patients with history of head trauma were excluded. Substance abuse was not used as an exclusion criterion; however, the rate of substance abuse was relatively low. Ninety-four patients (53 men and 41 women) were experiencing their first episode of illness and were neuroleptic naive at the time of admission; 73 of them were still unmedicated at the time of the neuropsychological assessment. The remaining 21 had been given medication prior to testing for relatively brief periods (median, 7 days; 14 were medicated for ≤8 days). When the 73 never-treated patients were analyzed separately, the results were identical to those for the larger group. Consequently, this report presents the results for the entire sample. Demographic and clinical characteristics are summarized in Table 1.

All patients were evaluated with the Comprehensive Assessment of Symptoms and History.18 All available sources of information (hospital records and interviews with patients, informants, nurses, and social workers) were used in completing the Comprehensive Assessment of Symptoms and History. All patients were diagnosed using either DSM-III-R or DSM-IV diagnostic criteria. Patients were evaluated weekly using the Scale for the Assessment of Negative Symptoms19 and the Scale for the Assessment of Positive Symptoms.20 Patients’ global psychotic symptoms (ie, delusions and hallucinations) and global negative symptoms (ie, affective flattening, alogia, avolition, and anhedonia) were in the mild to moderate range (mean [SD], 2.5 [1.3] and 2.4 [1.0], respectively). Their disorganized symptoms (ie, bizarre behavior and formal thought disorder) were in the questionable to mild range (mean [SD], 1.6 [1.0]).

Normal comparison subjects were recruited from the community through newspaper advertisements. These individuals were screened for psychiatric illnesses using a structured interview based on the Comprehensive Assessment of Symptoms and History.19 Exclusion criteria included diagnosis of schizophrenia spectrum disorders or affective illness, diagnosis of a schizophrenia spectrum disorder in first-degree relatives, medical illness that might affect cognition, history of neurological disorders, and past or present drug use or dependence. A group of 305 individuals (162 men and 143 women) under the age of 40 years was included in the analysis. Older individuals were excluded from this analysis to ensure age similarity among the patients. Demographic characteristics are summarized in Table 1.

COGNITIVE ASSESSMENT

Cognitive assessment occurred as soon as possible after admission. Patients were administered a comprehensive battery of tests that took approximately 4 hours to complete. Since the battery was updated periodically to integrate new research findings and to maximize coverage of all cognitive domains, sample size varied among tests. The battery included the Finger Tapping Test (average number of finger taps in 10 seconds),21 Trail Making Test (time to completion),22 Continuous Performance Test (number of hits),23 Benton Visual Retention Test (number of correct responses),24 Logical Memory Test, Wechsler Memory Scale–Revised (immediate recall, delayed recall, and percentage saving scores),25 Rey Auditory Verbal Learning Test (immediate recall, delayed recall, and recognition),26 Rey-Osterreith Complex Figure Test (copy, immediate recall, delayed recall, and percentage saving scores),27,28 Wisconsin Card Sorting Test (WCST) (number of categories and perseverative errors),29 Word Fluency Test (number of words generated in 3 minutes in response to the letters C, F, L),30 and Stroop Test (number correct on card 3 in 45 seconds and the calculated interference score).31 In addition, the following subscales from the WAIS-R were administered: digit span, digit symbol, vocabulary, information, comprehension, similarities, block design, object assembly, picture arrangement, and picture completion. Tests were administered by psychologists who were trained in standardized assessment and had experience working with patients with schizophrenia. They all had at least an undergraduate degree in psychology and were supervised by a psychologist with a PhD degree.

STATISTICAL ANALYSIS

Raw test scores were transformed into standard z scores using the means and SDs of age-stratified normal comparison individuals to control for age-related change in performance of cognitive measures. When applicable, tests were reverse-scored so that higher scores always reflected better performance. The schizophrenia group and the control group differed significantly in education. We covaried education to provide a conservative estimate of illness-related impairments. A series of analyses of covariance controlling for education were conducted on the neuropsychological test scores to evaluate the profiles. Group (patient vs control) was the between-group factor. A highly conservative Bonferroni correction was used to adjust the level of significance of all analyses (critical P = .002). All tests were 2-tailed. Since the F values in the analysis of covariance are heavily influenced by the sample size, which varied in this study, E’s were computed using normal controls’ SDs to measure the magnitude of the difference in performance between patients and controls on individual tests.

A follow-up analysis sequentially compared patients’ scores for a particular test with the mean of their scores on the remaining tests in the profile. This procedure allowed the determination of selectively more pronounced deficits. Bonferroni correction was used to adjust the level of significance of the contrast analysis. The E’s were computed to measure the magnitude of differences.

All of these studies to date examined performance on a large battery of tests but used summary scores of multiple tests to reflect a certain cognitive domain. Although important for data reduction, the use of a global...
As expected, there was a significant difference between patients and controls in education ($F_{1,305} = 76.13, P<.001$). There were no significant differences between the 2 groups in age or parental education.

### RESULTS

#### DEMOGRAPHICS AND NEUROPSYCHOLOGICAL COMPARISON

As expected, there was a significant difference between patients and controls in education ($F_{1,305} = 76.13, P<.001$). There were no significant differences between the 2 groups in age or parental education.

We compared the performance of the 21 patients who were briefly medicated prior to testing with that of those who had received no medication. There were no significant differences in their performance on any of the tests. Therefore, they were treated as one group in further analyses.

The means of the $z$ scores (adjusted for education) of the neuropsychological battery for normal controls and patient groups on individual test scores are summarized in Table 2. After Bonferroni adjustment (critical $P = .002$), patients performed significantly worse than controls on all tests except the saving scores of both the Logical Memory Test and the Rey-Osterreith Complex Figure Test (the ratio of delayed recall to immediate recall) and the Stroop Test interference score (Table 2).

The ESs of these differences were computed using the normal controls’ SDs. Table 3 lists these ESs. The differences between patients and controls were greatest on the WCST perseverative errors score (ES, 1.86), Rey Auditory Verbal Learning Test recognition score (ES, 1.70), WAIS-R digit symbol score (ES, 1.69), WAIS-R comprehension score (ES, 1.68), WAIS-R picture arrangement score (ES, 1.59), Continuous Performance Test number of hits score (ES, 1.56), and Rey Auditory Verbal Learning Test immediate recall score (ES, 1.53). The differences between patients and controls were least pronounced on the Rey-Osterreith Complex Figure Test savings score (ES, 0.09), Stroop Test interference score (ES, 0.29), and Logical Memory Test savings score (ES, 0.47).

Comparing the patients’ performance on each test with the mean of the remaining tests revealed significantly greater impairment in the WAIS-R digit symbol score.
controls substantial impairments in most aspects of cognition, as shown on neuropsychological studies of patients with first-episode schizophrenia. These findings are consistent with previous reports indicating that patients with schizophrenia are impaired on speeded cognitive tasks with and without a motor component, such as the Stroop Test. Relatively good performance was noted on the Trail Making Test, a speeded motor task, compared with other timed tests of memory and motor speed. Specifically, patients' performance on the Stroop Test part C score was very different from that of the control group (ES, 1.3). In contrast, performance on the Stroop Test part C reflects patterns of dysfunction that are primary and physiologically related to schizophrenia without the confounding factors of long-term treatment, illness, or hospitalization.

On memory tests, patients were as impaired on tests of immediate recall as they were on tests of delayed recall. The current findings converge with those previously reported by Paulsen et al., who suggested that the memory difficulties shown in patients with schizophrenia are primarily caused by deficits in encoding and retrieval rather than storage.

We also found evidence of impairment in speeded cognitive tasks with and without a motor component, such as the WAIS-R digit symbol test and the Stroop Test part C. Patients' relatively better performance on finger tapping, a speeded motor task, compared with other timed tests, suggests that poor performance on speeded tasks reflects bradyphrenia rather than bradykinesia. Consistent with this finding is the observation that patients with schizophrenia were impaired on the Stroop Test measuring reflecting cognitive speed. Specifically, patients' performance on the Stroop Test part C score was very different from that of the control group (ES, 1.3).

### Table 2. Comparisons Among Patients and Controls in Individual Test Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Effect Size</th>
<th>F</th>
<th>P</th>
<th>Mean (SD) Patients</th>
<th>No.</th>
<th>Mean (SD) Controls</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCST perseverative errors</td>
<td>1.86</td>
<td>49.66</td>
<td>&lt;.001</td>
<td>-1.91 (3.17)</td>
<td>84</td>
<td>-0.07 (0.99)</td>
<td>222</td>
</tr>
<tr>
<td>RAVLT recognition</td>
<td>1.70</td>
<td>29.12</td>
<td>&lt;.001</td>
<td>-1.73 (2.98)</td>
<td>56</td>
<td>-0.04 (1.00)</td>
<td>138</td>
</tr>
<tr>
<td>WAIS-R digit symbol</td>
<td>1.69</td>
<td>141.84</td>
<td>&lt;.001</td>
<td>-1.71 (1.10)</td>
<td>87</td>
<td>-0.06 (0.98)</td>
<td>248</td>
</tr>
<tr>
<td>WAIS-R comprehension</td>
<td>1.68</td>
<td>109.15</td>
<td>&lt;.001</td>
<td>-1.68 (1.47)</td>
<td>87</td>
<td>-0.09 (0.98)</td>
<td>248</td>
</tr>
<tr>
<td>WAIS-R picture arrangement</td>
<td>1.59</td>
<td>96.54</td>
<td>&lt;.001</td>
<td>-1.62 (1.57)</td>
<td>87</td>
<td>-0.04 (0.99)</td>
<td>248</td>
</tr>
<tr>
<td>CPT, No. of hits in 4 min</td>
<td>1.56</td>
<td>30.93</td>
<td>&lt;.001</td>
<td>-1.57 (2.28)</td>
<td>36</td>
<td>-0.02 (0.99)</td>
<td>128</td>
</tr>
<tr>
<td>RAVLT trial 5</td>
<td>1.53</td>
<td>56.88</td>
<td>&lt;.001</td>
<td>-1.70 (2.23)</td>
<td>89</td>
<td>-0.16 (1.00)</td>
<td>224</td>
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<tr>
<td>Trail Making Test time</td>
<td>1.41</td>
<td>9.20</td>
<td>.003</td>
<td>-1.31 (4.56)</td>
<td>88</td>
<td>-0.02 (0.91)</td>
<td>158</td>
</tr>
<tr>
<td>Logical Memory Test immediate recall</td>
<td>1.34</td>
<td>82.43</td>
<td>&lt;.001</td>
<td>-1.36 (1.14)</td>
<td>84</td>
<td>-0.05 (0.98)</td>
<td>224</td>
</tr>
<tr>
<td>WAIS-R vocabulary</td>
<td>1.33</td>
<td>57.19</td>
<td>&lt;.001</td>
<td>-1.34 (1.70)</td>
<td>87</td>
<td>-0.13 (0.91)</td>
<td>248</td>
</tr>
<tr>
<td>Stroop test part C</td>
<td>1.30</td>
<td>70.60</td>
<td>&lt;.001</td>
<td>-1.34 (1.30)</td>
<td>79</td>
<td>-0.06 (0.99)</td>
<td>239</td>
</tr>
<tr>
<td>Logical Memory Test delayed recall</td>
<td>1.28</td>
<td>72.14</td>
<td>&lt;.001</td>
<td>-1.30 (1.13)</td>
<td>81</td>
<td>-0.05 (0.98)</td>
<td>221</td>
</tr>
<tr>
<td>ROCFT copy</td>
<td>1.27</td>
<td>30.16</td>
<td>&lt;.001</td>
<td>-1.40 (2.87)</td>
<td>86</td>
<td>-0.05 (0.99)</td>
<td>245</td>
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<tr>
<td>BVRT, No. correct</td>
<td>1.26</td>
<td>17.59</td>
<td>&lt;.001</td>
<td>-1.29 (1.91)</td>
<td>45</td>
<td>-0.05 (0.98)</td>
<td>68</td>
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<tr>
<td>RAVLT delayed recall</td>
<td>1.22</td>
<td>54.70</td>
<td>&lt;.001</td>
<td>-1.21 (1.41)</td>
<td>82</td>
<td>-0.04 (0.96)</td>
<td>220</td>
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<tr>
<td>WAIS-R block design</td>
<td>1.11</td>
<td>51.43</td>
<td>&lt;.001</td>
<td>-1.15 (1.43)</td>
<td>87</td>
<td>-0.05 (0.99)</td>
<td>248</td>
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<tr>
<td>WAIS-R similarities</td>
<td>1.03</td>
<td>45.08</td>
<td>&lt;.001</td>
<td>-1.07 (1.36)</td>
<td>87</td>
<td>-0.07 (0.98)</td>
<td>248</td>
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<tr>
<td>WAIS-R object assembly</td>
<td>0.97</td>
<td>33.43</td>
<td>&lt;.001</td>
<td>-1.02 (1.68)</td>
<td>85</td>
<td>-0.05 (0.99)</td>
<td>245</td>
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<tr>
<td>WAIS-R picture completion</td>
<td>0.95</td>
<td>31.25</td>
<td>&lt;.001</td>
<td>-1.00 (1.71)</td>
<td>87</td>
<td>-0.07 (0.97)</td>
<td>248</td>
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<tr>
<td>ROCFT delayed recall</td>
<td>0.92</td>
<td>37.04</td>
<td>&lt;.001</td>
<td>-0.94 (1.26)</td>
<td>85</td>
<td>-0.04 (0.97)</td>
<td>238</td>
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<tr>
<td>WAIS-R information</td>
<td>0.91</td>
<td>35.18</td>
<td>&lt;.001</td>
<td>-0.96 (1.32)</td>
<td>88</td>
<td>-0.10 (0.95)</td>
<td>248</td>
</tr>
<tr>
<td>ROCFT immediate recall</td>
<td>0.86</td>
<td>30.54</td>
<td>&lt;.001</td>
<td>-0.87 (1.33)</td>
<td>86</td>
<td>-0.05 (0.97)</td>
<td>238</td>
</tr>
<tr>
<td>Finger Tapping Test, right hand</td>
<td>0.79</td>
<td>25.62</td>
<td>&lt;.001</td>
<td>-0.78 (1.29)</td>
<td>83</td>
<td>-0.01 (1.00)</td>
<td>209</td>
</tr>
<tr>
<td>Word Fluency Test</td>
<td>0.75</td>
<td>25.14</td>
<td>&lt;.001</td>
<td>-0.78 (1.25)</td>
<td>85</td>
<td>-0.05 (0.97)</td>
<td>240</td>
</tr>
<tr>
<td>WCST, No. of categories</td>
<td>0.75</td>
<td>24.34</td>
<td>&lt;.001</td>
<td>-0.79 (1.24)</td>
<td>84</td>
<td>-0.05 (0.99)</td>
<td>224</td>
</tr>
<tr>
<td>Finger Tapping Test, left hand</td>
<td>0.62</td>
<td>15.75</td>
<td>&lt;.001</td>
<td>-0.61 (1.30)</td>
<td>83</td>
<td>-0.00 (1.00)</td>
<td>209</td>
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<td>WAIS-R digit span</td>
<td>0.55</td>
<td>16.53</td>
<td>&lt;.001</td>
<td>-0.60 (0.96)</td>
<td>87</td>
<td>-0.05 (0.99)</td>
<td>248</td>
</tr>
<tr>
<td>Logical Memory Test savings</td>
<td>0.47</td>
<td>5.39</td>
<td>.02</td>
<td>-0.45 (2.10)</td>
<td>79</td>
<td>0.01 (0.98)</td>
<td>221</td>
</tr>
<tr>
<td>Stroop Test interference</td>
<td>0.29</td>
<td>4.47</td>
<td>.04</td>
<td>-0.32 (0.89)</td>
<td>79</td>
<td>-0.02 (1.00)</td>
<td>239</td>
</tr>
<tr>
<td>ROCFT savings</td>
<td>0.09</td>
<td>0.30</td>
<td>.58</td>
<td>-0.08 (1.73)</td>
<td>85</td>
<td>0.01 (1.00)</td>
<td>237</td>
</tr>
</tbody>
</table>

* WCST indicates Wisconsin Card Sorting Test; RAVLT, Rey Auditory Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised; CPT, Continuous Performance Test; BVRT, Benton Visual Retention Test; and ROCFT, Rey-Osterreith Complex Figure Test.

As expected, our large sample of neuroleptic-naive patients with first-episode schizophrenia was found to display substantial impairments in most aspects of cognition. These findings are consistent with previous neuropsychological studies of patients with first-episode schizophrenia as well as previous findings in studies of chronic schizophrenia. The presence of these deficits in a sample of patients very early in the course of illness, most of whom have never been medicated, reflects patterns of dysfunction that are primary and pathophysiologically related to schizophrenia without the confounding factors of long-term treatment, illness, or hospitalization.

On memory tests, patients were as impaired on tests of immediate recall as they were on tests of delayed recall. The current findings converge with those previously reported by Paulsen et al., who suggested that the memory difficulties shown in patients with schizophrenia are primarily caused by deficits in encoding and retrieval rather than storage.

We also found evidence of impairment in speeded cognitive tasks with and without a motor component, such as the WAIS-R digit symbol test and the Stroop Test part C. Patients' relatively better performance on finger tapping, a speeded motor task, compared with other timed tests, suggests that poor performance on speeded tasks reflects bradyphrenia rather than bradykinesia. Consistent with this finding is the observation that patients with schizophrenia were impaired on the Stroop Test measuring reflecting cognitive speed. Specifically, patients' performance on the Stroop Test part C score was very different from that of the control group (ES, 1.3). In contrast,
patients’ Stroop Test interference score was not significantly different from that of controls and was significantly higher than their mean score on the remaining tests (ES, 0.95). This indicates that patients’ poor performance on the Stroop Test is primarily caused by slowness in processing information.

Executive skills (eg, sequencing, organization, and flexibility) were among the areas that were highly impaired relative to controls. Similarly, we found evidence of more pronounced deficits in sustained attention and information and word fluency) also revealed discrepancies. Patients demonstrated more difficulties with a test that has a social cognition aspect (ie, comprehension) than with other verbal tasks (paired t test: t_{63} = 4.44, P <.001). Similarly, a paired t test revealed relatively worse performance on picture arrangement, a test that requires social cognition, compared with other WAIS performance subtests (ie, block design and picture completion) (t_{63} = 3.57, P <.001).

Symptoms were weakly correlated with some cognitive tasks. However, other tests were essentially unrelated to symptoms in first-episode schizophrenia.

Our findings of a generalized neurocognitive deficit should be interpreted in the context of the psychometric limitations of currently available neuropsychological measures. The inability to remove the possibly

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confounding factor of the differential discriminating power of the various tasks limits the interpretability of this and any other investigation of the neuropsychological functioning of patients with schizophrenia. Another limitation of this study could be that patients were tested while off medications during an acute episode. This might have made their performance worse than it would have after they had received treatment. This hypothesis could only be tested if patients were tested after their condition had stabilized after receiving treatment, which was outside the range of the current study. The inclusion of a subset of patients who were briefly treated prior to testing could be viewed as a potential limitation. However, we repeated the analyses on the never-medicated sample and the results were identical.

In general, these results emphasize a need for new models to understand schizophrenia. Old models are useful in explaining one cognitive deficit, but fall short of describing the complex and diverse phenomena of schizophrenia. Several research teams, including ours, have pursued this strategy and have proposed “candidate cognitive processes”37: eg, deficits in information processing, working memory, the inability to think in metarepresentation, and problems in representationally guided behavior.38-42 We have hypothesized that the cognitive disturbance in schizophrenia encompasses multiple functions, including learning, attention, speed of processing, and executive functions. To emphasize the diversity of the cognitive disturbance in schizophrenia and to call attention to the importance of disturbed cortical-cerebellar-thalamic-cortical circuits, we refer to the overarching deficit in schizophrenia as cognitive dysmetria.37 This concept emphasizes that schizophrenia reflects a disruption in fundamental circuitry in the brain, resulting in a generalized deficit in a basic cognitive process that leads to impairment in all cognitive systems and subsystems, including memory, attention, language, and executive functions. It highlights the importance of explaining the multiple symptoms of schizophrenia by identifying a basic mechanism and attempting to define its underlying neural circuits.

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